REMARKS

Claims 43-58 were pending in the subject application. Applicants by this Amendment have canceled claims 43-58 without disclaimer or prejudice and added new claims 59-64. Accordingly, claims 59-64 are now pending and presented for the Examiner's consideration.

Support for new claim 59 may be found, *inter alia*, on page 6, line 32 to page 7, line 1 of the subject specification.

Support for new claim 60 may be found, *inter alia*, on page 3 lines 11-13, on page 5, lines 27-32, and on page 6, line 32 to page 7, line 1 of the subject specification.

Support for new claim 61 may be found, *inter alia*, on page 4, lines 3-4 of the subject specification.

Support for new claim 62 may be found, *inter alia*, on page 3, lines 14-15 of the subject specification.

Support for new claim 63 may be found, *inter alia*, on page 5, lines 20-21 of the subject specification.

Support for new claim 64 may be found, *inter alia*, on page 3, lines 11-13 of the subject specification.

Rejection under 35 U.S.C. § 102 - Eisenberg

On page 2 of the April 9, 2003 Office Action, the Examiner rejected claims 9-15 [*sic*] as allegedly anticipated by Eisenberg. The Examiner offered no explanation for this rejection.

In response, applicant notes that the Examiner rejected claims 9-15 which were no longer pending. If, however, the Examiner intended to reject previously pending claim 43-58, these claims are canceled herein without prejudice. Thus, in either case, this ground of rejection is now moot.

To the extent Eisenberg is prior art to new claims 59-64, applicant points out that Eisenberg discloses the administration of 5 mg of oxandrolone per day, without disclosing the specific unit dosage amount. Solely for the purpose of this response, applicant will assume the highest possible dosage amount, i.e. 5 mg. In contrast, applicant's new claims 59-64 recite a pharmaceutical composition comprising oxandrolone in an amount of 7.5 mg or more. Thus, the claims are novel.

The subject matter of applicant's new claim 59-64 is also not obvious from the disclosure of Eisenberg. Eisenberg discloses the effects of several agents, including oxandrolone, on strontium excretion levels in patients with postmenopausal osteoporosis. Eisenberg concludes that the "results did not show whether the changes in urinary excretion rates induced by both gonadal steroids or glucocorticoids were attributable to effects on the kidney, on bone, or on both." Because Eisenberg discloses no benefit of treating postmenopausal osteoporosis patients with oxandrolone, one skilled in the art would have no motivation to make a pharmaceutical composition having oxandrolone in any amount. Certainly, one skilled in the art would have no motivation to make a pharmaceutical composition comprising oxandrolone in an amount of 7.5 mg or more, as claimed by applicant in new claims 59-64. Thus, the claims are not obvious.

Rejection under 35 U.S.C. § 103 - Pike et al. and Eisenberg

On page 3 of the April 9, 2003 Office Action, the Examiner rejected claims 43-58 as allegedly unpatentable over Pike et al. (U.S.

Patent 5,340,586) and Eisenberg. The Examiner's explanation pertained to canceled claims 43-58.

In response, as indicated above, applicant has canceled claims 43-58, without prejudice. To the extent Pike et al. and Eisenberg might relate to new claims 59-64, applicant respectfully directs the Examiner to the remarks pertaining to Eisenberg above.

More importantly, the disclosure of oxandrolone in Pike et al., however, is not prior art to applicant's claimed invention. Specifically, applicant's claims 59-64 are entitled to the October 20, 1992 filing date of U.S. Serial No. 07/963,469. However, while reviewing the claim to the benefit of the October 20, 1992 filing date, applicant has found that although the first paragraph of the subject specification properly reflects this claim to benefit pursuant to 35 U.S.C. § 120, the Declaration and Power of Attorney currently on file omits the claim to benefit of the October 20, 1992 date. Accordingly, applicant attaches hereto as **Exhibit A** the correct Declaration and Power of Attorney claiming benefit of the October 20, 1992 filing date of U.S. Serial No. 07/963,469. The attached Declaration and Power of Attorney is signed by Sim Fass on behalf of and as agent for the inventor, and has been accepted by the Office of Petitions in both the parent and the grandparent of the subject application as evidenced by a copy of a September 17, 2003 Letter in connection with the parent U.S. Serial No. 09/469,817 attached as **Exhibit B**, and a copy of a July 13, 1995 Decision On Renewed Petition Under 37 C.F.R. § 1.47(b) in the grandparent U.S. Serial No. 08/244,988 attached as **Exhibit C**.

Pike et al. is U.S. Patent No. 5,640,586 which issued from U.S. Serial No. 62,886, filed May 17, 1993, which in turn was a continuation-in-part of U.S. Serial No. 952,513, filed February 3, 1993, which in turn was a continuation-in-part of U.S. Serial

No. 684,612, filed April 12, 1991 and which is now U.S. Patent No. 5,211,952. Thus, in the chain of priority claimed by Pike et al., only U.S. Serial No. 684,612, filed April 12, 1991 which issued as U.S. Patent No. 5,211,952 can be prior art to applicant's claims. However, oxandrolone is not disclosed in U.S. Patent No. 5,211,952. Therefore, Pike et al. cannot be cited as prior art against applicant's invention as recited in new claims 59-64.

With respect to Pike et al., applicant further points out that oxandrolone is mentioned only once in the specification of Pike et al. in column 4, lines 35-36. However, neither a total daily amount of administration of oxandrolone is disclosed by Pike et al., nor a unit dosage amount of oxandrolone is disclosed by Pike et al. Accordingly, Pike et al., alone or in combination with Eisenberg, neither teach not suggest a pharmaceutical composition comprising oxandrolone in an amount of 7.5 mg or more, as claimed by applicant.

Supplemental Information Disclosure Statement

In accordance with their duty of disclosure under 37 C.F.R. § 1.56, applicant would like to direct the Examiner's attention to the following documents which are listed on the form PTO-1449 attached hereto as **Exhibit D**, and copies of which are attached hereto as **Exhibits 1-2**:

This Supplemental Information Disclosure Statement is being filed after the mailing of a first Office Action on the merits pursuant to 37 C.F.R. § 1.97(c). The fee set forth in 37 C.F.R. § 1.17(p) of $180.00 is included in the check submitted herewith. Accordingly, this Supplemental Information Disclosure Statement shall be considered.

1. U.S. Patent No. 6,090,799, issued July 18, 2000 to Berger (**Exhibit 1**).

2. U.S. Serial No. 09/469,817, filed December 22, 1999, now allowed, including a courtesy copy of the allowed claims (**Exhibit 2**).

In addition, applicant notes that the form PTO-1449 filed on January 18, 2002 in the subject application has not been returned to applicant with the Examiner's initials indicating consideration of the references cited therein. A copy of the form PTO-1449 filed on January 18, 2002 is attached hereto as **Exhibit 3**. Applicant respectfully requests that the Examiner consider the references, and then initial the citations of the references listed on the form PTO-1449 filed on January 18, 2002 and return a copy of the initialed form for applicant's files.

Summary

For the reasons set forth hereinabove, applicants respectfully request that the Examiner reconsider and withdraw the various grounds of objection and rejection set forth in the April 9, 2003 Office Action and earnestly solicit allowance of the now pending claims, i.e. claims 59-64.

No fee, other than the $950.00 fee for a three-month extension of time and the $180.00 fee for submission of the Supplemental Information Disclosure Statement, is deemed necessary in connection with the filing of this Amendment. However, if any other fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,

Gary J. Gershik

John P. White
Registration No. 28,678
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I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450

Gary J. Gershik 10/9/03

John P. White Date
Reg. No. 28,678
Gary J. Gershik
Reg. No. 39,992

Declaration and Power of Attorney

As a below-named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

A METHOD FOR AMELIORATING MUSCLE WEAKNESS/WASTING IN A PATIENT INFECTED WITH HUMAN IMMUNODEFICIENCY VIRUS-TYPE 1

the specification of which
(check one)

____ is attached hereto.

_X_ was filed on October 20, 1993 as

Application Serial No. PCT/US93/10063 U.S. Serial No. 08/244,988

and was amended on _____
(if applicable)

I hereby state that I have reviewed and understand the contents of the above-identified specification including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information of which I am aware which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations Section 1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s) Number	Country	Filing Date	Priority Claimed Yes	No
NONE				

I hereby claim the benefit under Title 35, United States Code, Section 120 of any United States Application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, Section 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, Sections 1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

Application Serial No.	*Filing Date*	*Status*
PCT/US93/10063	October 20, 1993	
07/963,469	October 20, 1992	

And I hereby appoint

John P. White (Reg. No. 28,678); Norman H. Zivin (Reg. No. 25,385); Thomas F. Moran (Reg. No. 16,579); Ivan S. Kavrukov (Reg. No. 25,161); Christopher C. Dunham (Reg. No. 30,141); Peter J. Phillips (Reg. No. 29,691); Richard S. Milner (Reg. No. 33,970); Matthew J. Golden (Reg. No. 35,161); Albert Wai-Kit Chan (Reg. No. 36,479); Matthew B. Tropper (Reg. No. 37,457); Lewis J. Kreisler (Reg. No. 38,522); Robert T. Maldonado (Reg. No. 38,232).

and each of them, all c/o Cooper & Dunham LLP, 1185 Avenue of the Americas, New York, New York 10036, *my attorneys, each with full power of substitution and revocation, to prosecute this application, to make alterations and amendments therein, to receive the patent, to transact all business in the Patent and Trademark Office connected therewith and to file any International Applications which are based thereon under the provisions of the Patent Cooperation Treaty.*

Please address all communications, and direct all telephone calls, regarding this application to

John P. White *Reg. No.* 28,678

Cooper & Dunham LLP
1185 Avenue of the Americas
New York, New York 10036
Tel. (212) 278-0400

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of sole or first joint inventor Joseph R. Berger (Sim Fass, on behalf of and as agent for)

Inventor's signature 

Citizenship United States of America *Date of signature* June 21, 1995

Residence 6460 S.W. 109th Street, Miami, Florida 33156

Post Office Address University of Kentucky-Annex 4, Chambers Building, Room 228E
Lexington, Kentucky 40536

Signed by Sim Fass, an authorized official of the assignee, BTG Pharmaceuticals Corp., on behalf of and as agent for Joseph R. Berger.

JPW

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Paper No. 9

JOHN P WHITE
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1185 AVENUE OF THE AMERICAS
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Received
Mail & JPW 9-23-03

In re Application of
Berger
Application No. 09/469,817
Filed: December 22, 1999
Attorney Docket No. 44657-AA-PCT-US/JPW/GJG
For: METHOD FOR AMELIORATING MUSCLE WEAKNESS/WASTING IN A PATIENT INFECTED WITH HUMAN IMMUNODEFICIENCY VIRUS-TYPE 1

LETTER

COPY MAILED

SEP 17 2003

OFFICE OF PETITIONS

Status Inquiry:
1/17/04
+
3/17/04
W.D.

This letter is in response to the petition under 37 CFR 1.47(b) filed on April 11, 2003

The petition is **GRANTED**.

In accordance with 37 CFR 1.63(d), petitioner has submitted a copy of the executed oath or declaration filed in Application No. 08/244,988, of which the instant filing is a continuation application. A copy of the decision, mailed on July 13, 1995, granting a petition to accord § 1.47 status to the prior application is present in the file of the above-identified application.

Petitioner never received a copy of the July 13, 1995 decision granting 47 status to the prior application. A copy of the July 13, 1995 decision is enclosed.

The above-identified application and papers have been reviewed and found in compliance with 37 CFR 1.47(b). This application is hereby accorded Rule 1.47(b) status. No fee has been or will be charged.

The Office will not forward notice of this application's filing to the non-signing inventor because notice regarding the filing of the prior application has already been sent to the non-signing inventor.

After this decision is mailed, the application will be forwarded to Publications Division.

Telephone inquiries related to this decision should be directed to the undersigned at 703-308-67212.

E. Shirene Willis

E. Shirene Willis
Senior Petitions Attorney
Office of Petitions

enclosure: copy of July 13, 1995 decision in application no. 08/244,988

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

Patent Cooperation Treaty
Legal Office

Address: Assistant Commissioner for Patents
Box PCT
Washington, D.C. 20231

13 JUL 1995

John P. White
Cooper & Dunham LLP
1185 Avenue of the Americas
New York, New York 10036

In re Application of	
Joseph R. BERGER	DECISION ON
Application No.: 08/244,988	
PCT No.: PCT/US93/10063	RENEWED PETITION
Int. Filing Date: 20 October 1993	
Priority Date: 20 October 1992	UNDER 37 CFR 1.47(b)
For: A METHOD FOR AMELIORATING MUSCLE WEAKNESS/WASTING IN A PATIENT INFECTED WITH HUMAN IMMUNODEFICIENCY VIRUS-TYPE 1	

This decision is in response to applicant's "RENEWED PETITION UNDER 37 C.F.R. §1.47(b)" filed on 22 June 1995 that seeks the acceptance of the application without the signature of the inventor Joseph R. Berger. Applicant's petition filed 17 April 1995 was dismissed in a decision dated 10 May 1995 because applicant did not present (1) an acceptable declaration and (2) a showing that such action is necessary to preserve the rights of the parties or to prevent irreparable damage.

Applicant has filed the following papers:

1) a renewed petition;

2) a declaration executed by Sim Fass, President, BTG Pharmaceutical Corporation, on behalf of Mr. Berger;

3) a showing that such action is necessary to preserve the rights of the parties or to prevent irreparable damage.

DISCUSSION

The application and papers have been reviewed and have been found to be in compliance with 37 CFR 1.47(b). The steps enumerated by Mr. Albert Wai-Kit Chan Noonan are sufficient to establish that the Mr. Berger is refuses to sign the declaration.

CONCLUSION

The petition under 37 CFR 1.47(b) is GRANTED.

The Application Division and the International Division are authorized to accept the application as a 37 CFR 1.47(b) application and to mail a filing receipt. The application will be given an international filing date of 20 October 1993 under 35 U.S.C. 363, and a date of 22 June 1995 under 35 U.S.C. 371(c) and 102(e).

As provided in 37 CFR 1.47(b), a notice of the filing of this application will be forwarded to the non-signing inventor at his last known addresses of record. Should such notice be returned undelivered, it must be returned to the PCT Legal Office and notice of the filing of the application will be published in the Official Gazette when said application is ready for issue and is returned to the International Division for review of its Section 1.47(b) status.

The application is not relived of its 37 CFR 1.47(b) status and must be returned to the PCT Legal Office after mailing any "Notice of Allowability" or "Notice of Allowance and Issue Fee Due" for review of its Section 1.47(b) status.

The application is being returned to the International Division for processing as the U.S. National Stage of the above-identified international application.

Leonard E. Smith
PCT Legal Examiner
PCT Legal Office

LES:ls

Form PTO-1449	U.S. Department of Commerce Patent and Trademark Office	Atty. Docket No. 44647-AAA-PCT-US/JPW/GJG	Serial No. 10/052,961
	INFORMATION DISCLOSURE CITATION (Use several sheets if necessary)	Applicants Joseph R. Berger	
		Filing Date January 18, 2002	Group

U.S. PATENT DOCUMENTS

Examiner Initial		Document Number	Date	Name	Class	Subclass	Filing Date if Appropriate
		6 0 9 0 7 9 9	7/18/2000	Berger			

FOREIGN PATENT DOCUMENTS

		Document Number	Date	Country	Class	Subclass	Translation	
							Yes	No

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

		U.S Serial No. 09/469,817, filed December 22, 1999, now allowed, including a courtesy copy of the allowed claims (Exhibit 2)

EXAMINER	DATE CONSIDERED

*EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609: Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

US006090799A

United States Patent [19]

Berger

[11] **Patent Number: 6,090,799**

[45] **Date of Patent: Jul. 18, 2000**

[54] **METHOD FOR AMELIORATING MUSCLE WEAKNESS/WASTING IN A PATIENT INFECTED WITH HUMAN IMMUNODEFICIENCY VIRUS-TYPE 1**

[75] Inventor: **Joseph R. Berger**, Miami, Fla.

[73] Assignee: **BTG Pharmaceuticals Corp.**, Iselin, N.J.

[21] Appl. No.: **08/244,988**

[22] PCT Filed: **Oct. 20, 1993**

[86] PCT No.: **PCT/US93/10063**

§ 371 Date: **Jun. 22, 1995**

§ 102(e) Date: **Jun. 22, 1995**

[87] PCT Pub. No.: **WO94/08590**

PCT Pub. Date: **Apr. 28, 1994**

[51] **Int. Cl.**[7] **A61K 31/56**

[52] **U.S. Cl.** **514/179**

[58] **Field of Search** 514/179

[56] **References Cited**

FOREIGN PATENT DOCUMENTS

0222385 2/1993 European Pat. Off. .

OTHER PUBLICATIONS

O'Shea et al 74 CA: 75106a 1971.

Endo 73 CA: 95098g 1970.

Primary Examiner—Russell Travers

Attorney, Agent, or Firm—John P. White; Cooper & Dunham LLP

[57] **ABSTRACT**

A method for attenuating the HIV-associated myopathy and muscle wasting associated with infection by human immunodeficiency virus-Type 1. Administration of oxandrolone in a daily dosage of about 2.5 to about 20 milligrams is described.

8 Claims, No Drawings

METHOD FOR AMELIORATING MUSCLE WEAKNESS/WASTING IN A PATIENT INFECTED WITH HUMAN IMMUNODEFICIENCY VIRUS-TYPE 1

This application a 371 of PCT US 93/10063 Oct. 20, 1993.

TECHNICAL FIELD

The invention relates to the use of oxandrolone to attenuate myopathy and muscle weakness/wasting associated with infection by human immune deficiency virus-Type 1.

BACKGROUND OF THE INVENTION

Human immunodeficiency virus (HIV) associated myopathy and/or muscle weakness/wasting is a relatively common clinical manifestation of acquired immunodeficiency syndrome (AIDS). This is one of a number of neuromuscular disorders associated with the disease. There is some evidence to indicate that direct HIV infection of muscle may be at least partly responsible, occasionally resulting in a polymyositis-like disorder. In addition, zidovudine (AZT), an antiviral agent that is used widely in the clinical management of AIDS, has been associated with a toxic myopathy, presumably related to an inhibition of mitochondrial metabolism. In any event, the loss of muscle mass commonly observed in AIDS victims negatively impacts muscle function, however caused.

Individuals with HIV-associated myopathy or muscle weakness or wasting typically experience significant weight loss, generalized or proximal muscle weakness, tenderness, and muscle atrophy. Laboratory tests of samples from such individuals often reveal elevated levels of enzymes associated with muscle degeneration and necrosis, such as creatine kinase, aldolase, and aspartate amino transferase. Electromyographic test results for individuals with HIV-associated myopathy are typically consistent with myopathic changes. Histopathologic tests may reveal muscle fiber necrosis associated with lymphocytic inflammatory infiltrates. In AZT myotoxicity, ragged red fibers are often observed.

Clinical management of HIV-associated myopathy and muscle weakness/muscle wasting varies. In individuals with AZT myopathy, withdrawal of this anti-retroviral agent may be associated with temporary improvement in strength and muscle bulk. Corticosteroid therapy, such as the administration of prednisone, has been occasionally successful when inflammatory infiltrates have been detected in muscle. However, a potential drawback to this approach is that corticosteroids, because of their immunosuppressant activity, may be harmful to individuals with AIDS who are already dangerously immunosuppressed as a consequence of the HIV infection.

Furthermore, corticosteroid use itself is associated with myopathies and an increased susceptibility to infections. Plasmapheresis has also been used with some success, although at least one patient has experienced, despite an increase in muscle strength, substantial weakness over a period of several weeks.

SUMMARY OF THE INVENTION

The present invention provides a method which employs oxandrolone (an anabolic steroid with weak androgenic activity) as an alternative approach to the clinical management of HIV-associated myopathy/muscle weakness/muscle wasting. Loss in muscle mass (wasting) is attenuated, and body weight can be more readily maintained in this manner. Such an approach has been applied successfully to improve strength, reverse weight loss, and provide an improved sense of well-being.

Importantly, no evidence of liver injury or other untoward side effects have been observed.

Oxandrolone preferably is administered orally; however, other routes of administration can be utilized as well.

The present method of ameliorating muscle weakness or muscle wasting in a patient infected with HIV comprises administering to the patient daily a sufficient amount of oxandrolone to attenuate the patient's rate of muscle mass loss. To this end, oxandrolone may be administered, orally or otherwise, in a daily dose in the range of about 2.5 to about 20 milligrams. However, the response of individual patients may vary and in some instances a daily dose greater than 20 mg may be required to achieve the desired response. The daily dose may be divided into unit doses of about 1 to about 5 milligrams each, administered to the patient three times per day at about eight-hour intervals.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

Oxandrolone (17-hydroxy-17-methyl-2-oxaandrostan-3-one) is a known compound that is commercially available. The preparation of oxandrolone is described, inter alia, in U.S. Pat. No. 3,128,283 to Pappo, which description is incorporated herein by reference.

Pharmacologically, oxandrolone is a synthetic anabolic steroid similar in structure to testosterone, but having a different, lesser androgenic/anabolic activity ratio. In addition, oxandrolone is unique among all other testosterone analogues in that it contains an oxygen atom instead of a methylene group at the 2-position of the phenanthrene nucleus. In addition, oxandrolone lacks a 4-ene function in its A-ring. The anabolic potency of oxandrolone, estimated as approximately 3 to 13 times that of testosterone, is believed to result form this unique structure.

Oxandrolone disposition and metabolism in man has been studied following oral administration of a 10 milligram dose. The study indicated that oxandrolone was rapidly and completely absorbed, yielding a mean peak plasma concentration of 417 micrograms of Oxandrolone per milliliter at 66 minutes. The plasma concentration of oxandrolone declined in a biphasic manner with a distribution half-life of approximately 30 minutes and an elimination half-life of 9.4 hours. Protein binding of oxandrolone was observed to be extensive.

In distinct contrast to other anabolic androgenic steroids such as methyltestosterone, fluoxymesterone, and micronized testosterone, oxandrolone taken orally is excreted mainly unchanged and unconjugated in urine. Urinary excretion of approximately 35 percent of an oral oxandrolone dose has been observed within 72 hours after ingestion. After 96 hours, approximately 65 percent of the administered oxandrolone dose was excreted in urine. Fecal excretion accounts for less than about 3 percent over the same time period.

Oxandrolone compositions, upon administration in accordance with this invention, ameliorate myopathy and muscle weakness in patients suffering from infections by human immunodeficiency virus-Type 1. Anabolic steroids, as a class, are known to stimulate appetite. Improved nutrition is important to individuals with AIDS who have experienced loss of lean body mass. Further, as a consequence of direct

interaction with androgen and/or glucocorticoid receptors in muscle, anabolic steroids promote muscle anabolism through both anabolic pathways and anticatabolic pathways.

Anabolic steroids, such as oxandrolone, also increase protein synthesis. For example, oxandrolone increased muscle protein synthesis in a study of acute uremic rats. Similarly, administration of oxandrolone preceded clinical improvement in appetite, cell mass, human growth, and weight for height in boys with chronic renal failure. These observations are consistent with anabolic activity. Oxandrolone may also stimulate the secretion of growth hormone and insulin-like growth factors.

In addition to producing beneficial direct anabolic action, oxandrolone is also believed to act as a delayed immunostimulant. In contrast, other appetite stimulants, such as dronabinol, that are currently under evaluation as appetite stimulants for AIDS patients can act as immunosuppressants in animals.

For purposes of administration in accordance with this invention, the active ingredient oxandrolone is combined with solid or liquid pharmaceutical carriers and formulated in unit dosage form using pharmacologically acceptable excipients, or dissolved or suspended in physiologically acceptable solvents or liquid vehicles for oral, percutaneous, or topical administration.

The overall daily dose of oxandrolone to provide a therapeutically effective amount in accordance with the method of this invention can be as low as about 2.5 milligrams and as high as about 20 milligrams, depending upon the pationt's response and the mode of administration.

The amount of the active ingredient within the aforementioned ranges that is to be administered depends upon the age, weight and condition of the patient, as well as on factors such as the frequency and route of administration. In formulating oxandrolone, it is recognized that there may be differences between the immediate and the long term response. To account for these changes, the specific dosage given to a particular patient is based also on the individual patient's response. Preferably, oxandrolone is orally administered to the patient daily for a time period in the range of about 2 weeks to about 6 months.

Attenuation of the rate of muscle mass loss in a patient can be ascertained by comparing the patient's rate of weight loss before oxandrolone therapy with that after the administration of oxandrolone has been commenced. Alternatively, or in addition, the patient's urinary nitrogen level can be monitored, a well-known expedient. A decrease in the patient's urinary nitrogen level is indicative of a decrease in muscle mass loss.

Similarly, the maintenance of a relatively stable patient's total body potassium level, as well as an increase in the patient's total body potassium level, upon oxandrolone administration indicates that a therapeutically effective amount of oxandrolone is being administered. A patient's total body potassium level can be monitored, for example, as described in Kotler et al., The American Journal of Clinical Nutrition, 42:1255–1265 (December 1985) and Pierson, Jr., et al., Am. J. Physiol., 246 (Renal Fluid Electrolyte Physiol. 15) :F234–F239 (1984).

The route of administration can be oral, percutaneous, transdermal, sublingual, buccal, intravenous, intramuscular, or the like. Of these, oral administration is preferred. The patient's daily dose of the active ingredient preferably is in the range of about 7.5 milligrams, but may exceed 20 milligrams based on clinical response. This daily dose can be given in tablet form as a single dose, or as plural divided doses, preferably 2 to 3 divided doses. The requisite daily dose can also be supplied continuously, for example, by a transdermal patch worn by the patient or intravenously. If the oxandrolone is administered orally, dosages in the range of about 2 to about 5 milligrams three to four times daily typically may be prescribed.

Oxandrolone tablets are manufactured using standard solid dose form technology in accordance with United States Pharmacopeia (USP) specifications (see, for example, The United States Pharmacopeia, 22nd Revision, pp. 981–982). Specifically, a typical 150-milligram tablet contains the following:

Oxandrolone, USP	2.5 mg
Corn Starch, NF	30.0 mg
Lactose NF (hydrous)	113.0 mg
Hydroxypropyl Methylcellulose, USP	3.0 mg
Magnesium Stearate	1.5 mg
	150.0 mg

The terms "unit dosage form" and "unit dose" as used in the present specification and claims refer to a physically discrete unit or units suitable as unitary doses for patients, each unit containing a predetermined quantity of the active ingredient calculated to produce the desired therapeutic effect in association with the pharmacologically acceptable carrier. The specifications for the unit dosage forms of this invention are dictated in part and are also dependent upon (a) the unique characteristics of the active ingredient and (b) the particular therapeutic effect to be achieved, as well as upon limitations inherent in the art of compounding such active ingredient for the therapeutic use disclosed in detail in this specification. Examples of suitable unit dosage forms in accordance with this invention are tablets, pills, powder packets, wafers, cachets, segregated multiples of any of the foregoing, transdermal patches, aliquots of injectables, and the like forms.

The primary response variables are patient's total body potassium, body weight, muscle mass, muscle strength, improvement in or increased appetite, and general sense of well-being. In addition, improvement in immune status (or at a minimum, no worsening of immune function) in response to oxandrolone is significant as well.

An important question regarding the use of any drug in combination with anti-retroviral therapy is whether drug interactions may occur that would diminish AZT efficacy or increase the frequency of severity of AZT-related adverse reactions. TABLE 1 compares various published pharmacological parameters for oxandrolone and AZT and illustrates important differences between the two drugs.

TABLE 1

Comparison of Selected Oxandrolone and AZT Pharmacology Parameters

Parameter	Oxandrolone	AZT
Oral Bioavailability	100%	65%
Tmax	1.1 hr	0.7 hr
Biological T1/2	9.4 hr	1.1 hr
Vd	578 ml/kg	>1400 ml/kg
Protein Binding	>95%	25–35%
Plasma Clearance	43 ml/kg/hr	>1300 ml/kg/hr
Metabolism	Little	Extensive

TABLE 1-continued

Comparison of Selected Oxandrolone and AZT Pharmacology Parameters

Parameter	Oxandrolone	AZT
Glucuronidation	Little	Substantial
Urinary Excretion	Extensive: primarily parent compound	Extensive: parent and glucuronide conjugated
Target Organ Toxicity	Liver (anabolic steroids as a class)	Hematopoietic system (e.g., anemia, granulocytopenia)
Known Drug Interactions	Anticoagulants: oral hypoglycemic agents: adrenal steroid when edema present	Drugs that may: (a) inhibit glucuronidation (e.g., aspirin, acetaminophen) or urinary excretion (e.g., probenecid); (b) adversely affect blood cell number and function; and (c) nephrotoxic or cytotoxic

Because oxandrolone is primarily protein bound, whereas AZT is primarily non-protein bound, oxandrolone will not compete appreciably with AZT for binding sites in plasma. Consequently, administration of oxandrolone to patients on AZT therapy is unlikely to alter the level of free AZT in the blood. Likewise, the administration of AZT is unlikely to alter the level of free oxandrolone in the blood. An oxandrolone-AZT drug interaction involving binding site displacement is, therefore, extremely unlikely.

AZT is rapidly metabolized and excreted in the urine—a significant quantity is excreted in the form of glucuronide conjugates. In sharp contrast, oxandrolone, perhaps due to presence of a lactone group and the absence of a 4-ene function in the A-ring, undergoes little hepatic metabolism and is excreted primarily unchanged and unconjugated in urine. Thus, in contradistinction to other drugs that may competitively inhibit glucuronidation and thereby potentially slow the rate of AZT metabolism, such as aspirin, acetaminophen, or indomethacin, the present active agent, oxandrolone, is not believed to affect AZT metabolism.

Furthermore, oxandrolone is neither nephrotoxic nor cytotoxic. Accordingly, oxandrolone is not expected to interfere with the renal excretion of AZT or its metabolites. To the contrary, oxandrolone has been safely and effectively used in patients with chronic renal disease to stimulate growth and increase lean body mass. In well-controlled studies of oxandrolone for the clinical management of critically ill patients with acute alcoholic hepatitis, oxandrolone administered at daily doses of up to 80 mg/day for four weeks and 40 mg/day for eight weeks did not result in any drug-related nephrotoxicity.

While it is known that anabolic androgenic steroids have been associated with potentially life-threatening forms of liver disease, including peliosis hepatis, cholestatic jaundice, and hepatocellular neoplasms, specific reports in the medical literature regarding liver disease in oxandrolone-treated patients, at the dosages proposed for use in the clinical management of HIV associated muscle weakness/wasting (i.e., about 2.5 to about 20 mg/day) are rare.

Oxandrolone and AZT have different mechanisms of action. They also function in different sites of cellular action at the receptor level. Oxandrolone functions via interaction with androgen and glucocorticoid receptors, whereas AZT, once phosphorylated, acts to inhibit HIV reverse transcription. Thus, competitive inhibition of AZT by oxandrolone at the cellular level also is considered unlikely.

Neither has oxandrolone been associated with anemia or granulocytopenia, two frequently occurring and potentially serious side effects associated with AZT therapy. To the contrary, anabolic androgenic steroids have been used clinically to stimulate ethyropoiesis in hypoanemias, aplastic anemias, hemolytic anemias, renal anemias, anemias due to cytotoxic therapy, and various leukemias. It has been reported recently that androgens augment beneficial effects of erythropoietin in the treatment of anemia resulting from end-stage renal disease.

Data derived from animal models and human clinical studies indicate that anabolic steroids are unlikely to suppress immune function in patients infected with HIV. For example, anabolic steroids can stimulate granulopoiesis in mice, as evidenced by stimulation of granulocytic colony-forming cells derived from spleen and bone marrow. Similarly, an anabolic steroid known as nandrolone decanonate enhanced macrophage activity and cell-mediated immunity in patients with uterine cervical cancer when administered parentally. In related studies, anabolic steroids increased peripheral lymphocyte and monocyte counts, Immunoglobin G (IgG) levels, and PHA-blastoid transfromation of peripheral lymphocytes. In those studies, β_2-microglobulin levels simultaneously decreased.

IgG is one of a class of antibodies secreted by B cells (i.e., B-lymphocytes) in response to an antigenic challenge (e.g., foreign protein like that from bacteria). In the case of HIV infection, humoral immune function (i.e., B-cell mediated) is significantly impaired. Accordingly, when HIV-infected individuals are challenged with a specific antigen, the typical response of B-cell proliferation, differentiation and secretion of antibodies (e.g., IgG) is diminished or absent. This decline in humoral immune function coupled with defects in cellular immune (i.e., T-cell) function contributes to the overall failure of the immune system to respond in an appropriate manner to challenge. B-cells in AIDS victims are, by mechanisms unknown, hyperstimulated to secrete large amounts of immunoglobulins that make the humoral system refractory to new antigens. The result is that the patient's system no longer recognizes new antigens and does not respond.

In animal studies in which anabolic steroids have been reported to increase IgG and PHA-blastoid activity, these changes occurred as a result of immune system stimulation, and are positive responses. β-microglobin is a cell surface protein that is found on all nucleated calls and it is released into the serum during cell turnover. Generally, β-microglobulin is considered a marker of infectious, inflammatory, malignant and autoimmune disease activity. In several AIDS studies, β-microglobulin levels correlated with disease progression and T4 (T-helper) cell counts. In the case of therapy with oxandrolone, for example, a decrease in β-microglobulin levels is desirable. Thus, animal data showing reduced plasma levels of β-microglobulin in response to anabolic steroids is evidence of a positive effect and suggestive of similar activity in man.

Accordingly, there are no reasons to believe that the administration of an anabolic steroid in general and oxandrolone in particular would have adverse effects on the immune system. Generally, the target organ of toxicity for these drugs is the liver—probably because this is where most are metabolized. Oxandrolone, however, has a remarkably good safety profile in man as a likely consequence of its resistance to hepatic metabolism; an oral dose is excreted primarily in urine as the parent compound, as stated hereinabove.

Data from clinical trials in patients with severe alcoholic liver disease provide further evidence that oxandrolone is

not likely to suppress immune function in patients with HIV infection. Ethanol abuse is associated with loss of lymphocyte functions, particularly T-cell dependent immune responses. Previous researchers have observed that oxandrolone significantly improved lymphocyte number in patients with severe alcoholic hepatitis. Because the loss of lymphocytic function by alcoholic liver disease parallels, to a significant degree, the loss of T-cell function due to HIV infection, it is reasonable to hypothesize that oxandrolone will increase the T-Cell function of HIV-infected patients.

Therefore, these data from laboratory animals and human studies indicate that suppression of the immune system by anabolic steroids, such as oxandrolone, is unlikely. Nonetheless, subjects undergoing oxandrolone therapy, as a precaution, should be monitored for changes in lymphocyte number, particularly CD4+ and CD8+, as is routinely done for patients who undergo steroid therapy.

In summary, based on the differences between AZT and oxandrolone with respect to pharmacokinetics, metabolism, reported drug interactions, mechanisms of action, and reported toxicities, oxandrolone and AZT can be safely used in combination for subjects infected with the Type-1 HIV virus and suffering from HIV-associated myopathy. The use of oxandrolone in patients on AZT therapy is, on the basis of known drug interactions, also consistent with current FDA-approved labeling for AZT and oxandrolone.

The following example demonstrates the effectiveness of oxandrolone in attenuating the effects of HIV-associated muscle weakness or muscle wasting in an AIDS patient.

EXAMPLE

A patient, a thirty-two year old homosexual man, known to be HIV-seropositive since February 1989, noted difficulty opening drawers and bottles in May 1989. The patient weakened progressively and, during a physical examination in September 1989, demonstrated by confrontation testing the weakness of neck flexion and proximal limbs. However, his muscle stretch reflexes remained normal. Laboratory tests showed the patient's creatine kinase level to be 286 International Units per liter, much higher than the normally observed range for creatine kinase of about 40–200 Units per liter.

Zidovudine (azidothymidine or AZT) was initiated at 500 milligrams daily, but the patient's strength continued to decline through February 1990. He complained of an inability to ascend a flight of stairs. The patient exhibited greater weakness and atrophy of neck flexors and extremity muscles during another physical examination performed at this time. An electromyogram revealed a decrease of amplitude and duration of the patient's motor unit potentials and increased recruitment in selected muscles of his right upper extremity. The patient's creatine kinase tested at 456 Units per liter. A muscle biopsy revealed numerous myofibers, abundant ragged red fibers, and numerous eosinophilic inclusions. Round cell inflammatory infiltrates were also noted. In light of these developments, the zidovudine treatment was terminated.

Substantial improvement initially followed the discontinuation of zidovudine. However, because of a subsequent continued and progressive weakness rendering it difficult for the patient to ascend or descend a flight of stairs, a prednisone therapy (60 mg daily) was initiated. No significant improvement accompanied the use of prednisone.

Thereafter, a trial period of oral oxandrolone administration (2.5 milligrams, three times daily, in tablet form) was initiated. Within two weeks of the initiation of the oxandrolone therapy, the patient noted an improved sense of well being, became stronger, and gained weight. Within one month, he was able to ascend and descend stairs without problems. Confrontation testing revealed nearly normal strength. The patient's weight increased from 115 pounds to 130 pounds. The patient's muscle atrophy was alleviated as well. Liver functions were closely monitored for signs of elevation, but undesirable side effects were not detected.

After several months of the aforementioned therapy with oxandrolone, the patient was no longer able to obtain oxandrolone for use as a medication. Weakness and weight loss ensued. Trials of other anabolic preparations, specifically stanazol and oxymethalone, did not return the patient to his previous levels of function and strength.

The EXAMPLE demonstrates that oxandrolone can be a beneficial alternative for clinical management of HIV-associated myopathy and muscle weakness and wasting.

It is intended that the foregoing description is by way of illustration only and is not to be construed as limiting the invention in any way except in the spirit and scope of the appended claims.

What is claimed is:

1. A method for ameliorating HIV-associated myopathy and muscle weakness in an AIDS patient which comprises orally administering oxandrolone to the AIDS patient in a daily dosage of between about 2.5 to about 7.5 milligrams.

2. The method in accordance with claim **1** wherein the daily dosage of the oxandrolone is about 7.5 milligrams.

3. The method in accordance with claim **1** wherein the oxandrolone is administered to said patient as a unit dose of about 1 to about 2.5 milligrams three times per day at about eight-hour intervals.

4. The method in accordance with claim **1** wherein the oxandrolone is administered in the form of a tablet.

5. The method in accordance with claim **1** wherein administration is continued over a period of about 2 weeks.

6. The method in accordance with claim **1** wherein administration is continued over a period of about 2 weeks.

7. The method in accordance with claim **3** wherein administration is continued over a period of about 2 weeks.

8. A method for ameliorating HIV-associated myopathy and muscle wasting in an AIDS patient which comprises orally administering a therapeutically effective amount of oxandrolone to the AIDS patient daily for a time period of about 2 weeks.

* * * * *

Dkt. 44657-AA-PCT-US/JPW/JHB

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Joseph R. Berger

Serial No. : Not Yet Known

Filed : Herewith

For : A METHOD FOR AMELIORATING MUSCLE WEAKNESS/WASTING IN A PATIENT INFECTED WITH HUMAN IMMUNODEFICIENCY VIRUS-TYPE 1

1185 Avenue of the Americas
New York, New York 10036
December 22, 1999

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

PRELIMINARY AMENDMENT AND INFORMATION DISCLOSURE STATEMENT DIRECTED TO THE ACCOMPANYING CONTINUATION APPLICATION UNDER 37 C.F.R 1.53(b)

Applicants request that the following amendments be made in the above-identified application.

In the Specification:

Page 1, line 5, before the paragraph "Technical Field" please insert the following as a separate paragraph:

> --This is a continuation of application U.S. Serial No. 08/244,988, filed June 22, 1995, now allowed, which is a §371 of PCT International Application No PCT/US93/10063, filed 20 October, 1993, claiming priority of U.S. Serial No. 07/963,469, filed October 20, 1992.--

In the Claims:

Please cancel claims 1-42 without prejudice to applicant's right to pursue the subject matter of these claims in a subsequent application.

Please add new claims 43-78 as follows:

--43. (New) A method for ameliorating HIV-associated myopathy and muscle wasting in an AIDS patient which comprises administering a therapeutically effective amount of oxandrolone to the AIDS patient.

--44. (New) The method in accordance with claim 43 wherein the therapeutically effective amount comprises a daily dosage of between about 2.5 to about 30 milligrams.

--45. (New) The method in accordance with claim 43 wherein the therapeutically effective amount comprises a daily dosage of between about 2.5 to about 20 milligrams.

--46. (New) The method in accordance with claim 45 wherein the daily dosage is about 20 milligrams.

--47. (New) The method in accordance with claim 45 wherein the daily dosage is about 15 milligrams.

--48. (New) The method in accordance with claim 43 wherein the oxandrolone is administered orally.

--49. (New) The method in accordance with claim 48 wherein the oxandrolone is administered in the form of a tablet.

--50. (New) The method in accordance with claim 44 wherein the oxandrolone is administered orally.

--51. (New) The method in accordance with claim 50 wherein the oxandrolone is administered in the form of a tablet.

-- 52. (New) The method in accordance with claim 45 wherein the oxandrolone is administered orally.

--53. (New) The method in accordance with claim 52 wherein the oxandrolone is administered in the form of a tablet.

--54. (New) The method in accordance with claim 46 wherein the oxandrolone is administered orally.

--55. (New) The method in accordance with claim 54 wherein the oxandrolone is administered in the form of a tablet.

--56. (New) The method in accordance with claim 47 wherein the oxandrolone is administered orally.

--57. (New) The method in accordance with claim 56 wherein the oxandrolone is administered in the form of a tablet.

--58. (New) The method in accordance with claim 43 wherein the oxandrolone is administered daily for a time period in the range of about two weeks to about six months.

--59. (New) The method in accordance with claim 48 wherein the oxandrolone is administered daily for a time period in the range of about two weeks to about six months.

--60. (New) The method in accordance with claim 50 wherein the oxandrolone is administered daily for a time period in the range of about two weeks to about six months.

--61. (New) The method in accordance with claim 52 wherein the oxandrolone is administered daily for a time period in the range of about two weeks to about six months.

--62. (New) The method in accordance with claim 54 wherein the oxandrolone is administered daily for a time period in the range of about two weeks to about six months.

--63. (New) The method in accordance with claim 56 wherein the oxandrolone is administered daily for a time period in the range of about two weeks to about six months.

--64. (New) The method in accordance with claim 43 wherein the oxandrolone is administered percutaneously.

--65. (New) The method in accordance with claim 43 wherein the oxandrolone is administered intravenously.

--66. (New) The method in accordance with claim 43 wherein the oxandrolone is administered intramuscularly.

--67. (New) The method in accordance with claim 43 wherein the oxandrolone is administered sublingually.

--68. (New) The method in accordance with claim 43 wherein the oxandrolone is administered transdermally.

--69. (New) The method in accordance with claim 43 wherein the oxandrolone is administered in a unit dose of about 2 to about 5 milligrams three times daily.

--70. (New) The method in accordance with claim 44 wherein the oxandrolone is administered in a unit dose of about 2 to about 5 milligrams three times daily.

--71. (New) The method in accordance with claim 45 wherein the oxandrolone is administered in a unit dose of about 2 to about 5 milligrams three times daily.

--72. (New) The method in accordance with claim 46 wherein the oxandrolone is administered in a unit dose of about 2 to about 5 milligrams three times daily.

--73. (New) The method in accordance with claim 47 wherein the oxandrolone is administered in a unit dose of about 2 to about 5 milligrams three times daily.

--74. (New) The method in accordance with claim 43 wherein the oxandrolone is administered in a unit dose of about 1 to about 5 milligrams three or four times daily.

--75. (New) The method in accordance with claim 44 wherein the oxandrolone is administered in a unit dose of about 1 to about 5 milligrams three or four times daily.

--76. (New) The method in accordance with claim 45 wherein the oxandrolone is administered in a unit dose of about 1 to about 5 milligrams three or four times daily.

--77. (New) The method in accordance with claim 46 wherein the oxandrolone is administered in a unit dose of about 1 to about 5 milligrams three or four times daily.

--78. (New) The method in accordance with claim 47 wherein the oxandrolone is administered in a unit dose of about 1 to about 5 milligrams three or four times daily.

REMARKS

The subject application is a continuation of U.S. Serial No. 08/244,988 filed June 22, 1995. An Official Notice of Allowance was issued on July 8, 1999 in connection with U.S. Serial No. 08/244,988. The Notice of Allowance indicated that the Issue Fee was due on October 8, 1999. The Issue Fee was paid in a timely manner, but U.S. Serial No. 08/244,988 has not yet issued as a U.S. patent as of the filing of the subject application. Accordingly, U.S. Serial No. 08/244,988 is pending and the subject application is co-pending therewith for purposes of 35 U.S.C. §120.

Applicant maintains that the amendment to the specification presents no issue of new matter and is fully supported by the specification. Applicant has amended the specification to incorporate a reference to the parent application, U.S. Serial No. 08/244,988, filed June 22, 1995, in accordance with 35 U.S.C. §120, and to provide an updated status of the prior related applications.

By this Preliminary Amendment, claims 1-42 have been canceled without prejudice to Applicant's right to pursue the subject matter of these claims in a subsequent application and new claims 43-78 have been added. Accordingly, upon entry of this Amendment, claims 43-78 will be pending and under examination.

Support for new claim 43 may be found throughout the

specification and inter alia, on page 2, lines 27-33, and in claim 1 as originally filed. Support for new claim 44 may be found inter alia in claims 2 and 30 as originally filed.

Support for new claim 45 may be found inter alia on page 3, line 12. Support for new claim 46 may be found inter alia on page 6, line 34. Support for new claim 47 may be found inter alia in claim 4 as originally filed.

Support for new claims 48, 50, 52, 54 and 56 may be found inter alia on page 6, lines 29-32, and claims 11 and 39 as originally filed. Support for new claims 49, 51, 53, 55 and 57 may be found inter alia on page 7, lines 9-20, and claims 12 and 40 as originally filed.

Support for new claims 58 - 63 may be found inter alia on page 6, line 9, and claims 41 and 42 as originally filed. Support for new claims 64 - 68 may be found inter alia on page 6, lines 29 - 32, and claims 34 - 38 as originally filed.

Support for new claims 69 - 73 may be found inter alia on page 7, lines 5 - 8. Support for new claims 74 - 78 may be found inter alia on page 3, lines 16 - 19 and claim 33 as originally filed.

Applicant was the first to use oxandrolone to ameliorate HIV-associated myopathy and muscle wasting in AIDS patients. This was confirmed by the Examiner when he issued the parent application, U.S. Serial No. 08/244,988, filed June 22, 1995; with the Notice of Allowance dated July 8,1999 for the parent application, the Examiner attached a statement entitled `Reasons for Allowance' in which the Examiner stated: "An exhaustive literature search failed to produce any reference to the claimed compounds for the use herein claimed. Although some compounds claimed by Applicant reside in the prior (*sic*), the prior art

fails to state, or suggest the use herein claimed."

Applicant is therefore entitled to a claim (claim 43) commensurate in breadth to his discovery, and not limited to a specific dosage. Additionally, Applicant is certainly entitled to claims reciting dosages which have specific support in the specification (claims 44 - 47 and 69 - 78), and also to claims 48 - 57 which recite the preferred mode of administration. Furthermore, Applicant is also entitled to claims reciting the time period of administration contemplated in the specification (claims 58 - 63), and also to claims 64 - 68 which recite the additional modes of administration contemplated in the specification.

In view of the preceding remarks, Applicant believed that newly filed claims 43 - 78 define patentable subject matter, and earnestly solicits allowance of these claims.

Information Disclosure Statement

In accordance with their duty of disclosure under 37 C.F.R. § 1.56 and § 1.97 (a)-(b), applicants would like to direct the Examiner's attention to the references which are listed on the attached Form PTO-1449 (**Exhibit 1**), including the following references attached hereto as **Exhibits 2-8**:

1. Aroonsakul, Chemical Abstracts, Vol. 115: 151902q, 1988 (**Exhibit 2**);

2. Boris, et al.,Chemical Abstracts, Vol. 74: 72305d, 1971 (**Exhibit 3**);

3. Chicago Tribune, September 20, 1991, North Sports Final edition, Business Section, page 1 (**Exhibit 4**);

4. Kopera, H. Acta Endocrinologica 1985, Supplementum 271, pp. 11-18 (**Exhibit 5**);

5. Lone, et al., Chemical Abstracts, Vol. 107: 174950c, 1987 (**Exhibit 6**);

6. Martindale, The Extra Pharmacopoeia, The Pharmaceutical Press, London, Reynolds, et al., Eds., p.1430 (1982) (**Exhibit 7**);

7. PR Newswire, 0828P8715, August 28, 1991 "Gynex obtains international rights to drug to treat for growth disorders, AIDS" (**Exhibit 8**).

Applicants would like to direct the Examiner's attention to the following references which are listed on the attached Form PTO-1449 (**Exhibit 1**) and which were previously cited in connection with the prosecution of U.S. Serial Number 08/244,988 from which the subject application claims benefit under 35 U.S.C. §120. According to 37 C.F.R. §1.98(d), copies of patents or publications that were previously cited by, or submitted to, the Office in connection with such prior applications need not accompany the Information Disclosure Statement. Accordingly, copies of the following references are not attached to this Information Disclosure Statement:

1. European Patent Specification, Publication No. 0 222 385 B1, published February 3, 1993;

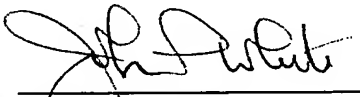
2. Endo, Chemical Abstracts, Vol. 73: 95098g, 1970;

3. O'Shea, et al., Chemical Abstracts, Vol. 74: 75106a, 1971; and

4. Physicians' Desk Reference (1988), 42nd Edition, cover page and pages 1975-1976;

No fee, other than the enclosed fee of $524.00 for filing the subject application, is deemed necessary in connection with the filing of this Preliminary Amendment. However, if additional any fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,



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(54) Title: A METHOD FOR AMELIORATING MUSCLE WEAKNESS/WASTING IN A PATIENT INFECTED WITH HUMAN IMMUNODEFICIENCY VIRUS-TYPE 1

(57) Abstract

A method for attenuating the HIV-associated myopathy and muscle wasting associated with infection by human immunodeficiency virus-Type 1. Administration of oxandrolone in a daily dosage of about 2.5 to about 20 milligrams is described.

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A METHOD FOR AMELIORATING MUSCLE WEAKNESS/WASTING IN A PATIENT INFECTED WITH HUMAN IMMUNODEFICIENCY VIRUS-TYPE 1

Technical Field

The invention relates to the use of oxandrolone to attenuate myopathy and muscle weakness/wasting associated with infection by human immunodeficiency virus-Type 1.

Background of the Invention

Human immunodeficiency virus (HIV) associated myopathy and/or muscle weakness/wasting is a relatively common clinical manifestation of acquired immunodeficiency syndrome (AIDS). This is one of a number of neuromuscular disorders associated with the disease. There is some evidence to indicate that direct HIV infection of muscle may be at least partly responsible, occasionally resulting in a polymyositis-like disorder. In addition, zidovudine (AZT), an antiviral agent that is used widely in the clinical management of AIDS, has been associated with a toxic myopathy, presumably related to an inhibition of mitochondrial metabolism. In any event, the loss of muscle mass commonly observed in AIDS victims negatively impacts muscle function, however caused.

Individuals with HIV-associated myopathy or muscle weakness or wasting typically experience significant weight loss, generalized or proximal muscle weakness, tenderness, and muscle atrophy. Laboratory tests of samples from such individuals often reveal elevated levels of enzymes associated with muscle degeneration and necrosis, such as creatine kinase, aldolase, and aspartate amino transferase. Electromyographic test results for individuals with HIV-associated myopathy are typically consistent with

myopathic changes. Histopathologic tests may reveal muscle fiber necrosis associated with lymphocytic inflammatory infiltrates. In AZT myotoxicity, ragged red fibers are often observed.

Clinical management of HIV-associated myopathy and muscle weakness/muscle wasting varies. In individuals with AZT myopathy, withdrawal of this anti-retroviral agent may be associated with temporary improvement in strength and muscle bulk. Corticosteroid therapy, such as the administration of prednisone, has been occasionally successful when inflammatory infiltrates have been detected in muscle. However, a potential drawback to this approach is that corticosteroids, because of their immunosuppressant activity, may be harmful to individuals with AIDS who are already dangerously immunosuppressed as a consequence of the HIV infection.

Furthermore, corticosteroid use itself is associated with myopathies and an increased susceptibility to infections. Plasmapheresis has also been used with some success, although at least one patient has experienced, despite an increase in muscle strength, substantial weakness over a period of several weeks.

Summary of the Invention

The present invention provides a method which employs oxandrolone (an anabolic steroid with weak androgenic activity) as an alternative approach to the clinical management of HIV-associated myopathy/muscle weakness/muscle wasting. Loss in muscle mass (wasting) is attenuated, and body weight can be more readily maintained in this manner. Such an approach has been applied successfully to improve strength, reverse weight loss, and provide an improved sense of well-being.

Importantly, no evidence of liver injury or other untoward side effects have been observed.

Oxandrolone preferably is administered orally; however, other routes of administration can be utilized as well.

The present method of ameliorating muscle weakness or muscle wasting in a patient infected with HIV-1 comprises administering to the patient daily a sufficient amount of oxandrolone to attenuate the patient's rate of muscle mass loss. To this end, oxandrolone may be administered, orally or otherwise, in a daily dose in the range of about 2.5 to about 20 milligrams. However, the response of individual patients may vary and in some instances a daily dose greater than 20 mg may be required to achieve the desired response. The daily dose may be divided into unit doses of about 1 to about 5 milligrams each, administered to the patient three times per day at about eight-hour intervals.

Detailed Description of the Preferred Embodiment

Oxandrolone (17-hydroxy-17-methyl-2-oxaandrostan-3-one) is a known compound that is commercially available. The preparation of oxandrolone is described, inter alia, in U. S. Patent No. 3,128,283 to Pappo, which description is incorporated herein by reference.

Pharmacologically, oxandrolone is a synthetic anabolic steroid similar in structure to testosterone, but having a different, lesser androgenic/anabolic activity ratio. In addition, oxandrolone is unique among all other testosterone analogues in that it contains an oxygen atom instead of a methylene group at the 2-position of the phenanthrene nucleus. In addition, oxandrolone lacks a 4-ene function in its A-ring. The anabolic potency of oxandrolone, estimated as

approximately 3 to 13 times that of testosterone, is believed to result form this unique structure.

Oxandrolone disposition and metabolism in man has been studied following oral administration of a 10 milligram dose. The study indicated that oxandrolone was rapidly and completely absorbed, yielding a mean peak plasma concentration of 417 micrograms of oxandrolone per milliliter at 66 minutes. The plasma concentration of oxandrolone declined in a biphasic manner with a distribution half-life of approximately 30 minutes and an elimination half-life of 9.4 hours. Protein binding of oxandrolone was observed to be extensive.

In distinct contrast to other anabolic androgenic steroids such as methyltestosterone, fluoxymesterone, and micronized testosterone, oxandrolone taken orally is excreted mainly unchanged and unconjugated in urine. Urinary excretion of approximately 35 percent of an oral oxandrolone dose has been observed within 72 hours after ingestion. After 96 hours, approximately 65 percent of the administered oxandrolone dose was excreted in urine. Fecal excretion accounts for less than about 3 percent over the same time period.

Oxandrolone compositions, upon administration in accordance with this invention, ameliorate myopathy and muscle weakness in patients suffering from infections by human immunodeficiency virus-Type 1. Anabolic steroids, as a class, are known to stimulate appetite. Improved nutrition is important to individuals with AIDS who have experienced loss of lean body mass. Further, as a consequence of direct interaction with androgen and/or glucocorticoid receptors in muscle, anabolic steroids promote muscle

anabolism through both anabolic pathways and anticatabolic pathways.

Anabolic steroids, such as oxandrolone, also increase protein synthesis. For example, oxandrolone increased muscle protein synthesis in a study of acute uremic rats. Similarly, administration of oxandrolone preceded clinical improvement in appetite, cell mass, linear growth, and weight for height in boys with chronic renal failure. These observations are consistent with anabolic activity. Oxandrolone may also stimulate the secretion of growth hormone and insulin-like growth factors.

In addition to producing beneficial direct anabolic action, oxandrolone is also believed to act as a delayed immunostimulant. In contrast, other appetite stimulants, such as dronabinol, that are currently under evaluation as appetite stimulants for AIDS patients can act as immunosuppressants in animals.

For purposes of administration in accordance with this invention, the active ingredient oxandrolone is combined with solid or liquid pharmaceutical carriers and formulated in unit dosage form using pharmacologically acceptable excipients, or dissolved or suspended in physiologically acceptable solvents or liquid vehicles for oral, percutaneous, or topical administration.

The overall daily dose of oxandrolone to provide a therapeutically effective amount in accordance with the method of this invention can be as low as about 2.5 milligrams and as high as about 20 milligrams, depending upon the patient's response and the mode of administration.

The amount of the active ingredient within the aforementioned ranges that is to be administered depends upon the age, weight and condition of the patient, as

well as on factors such as the frequency and route of administration. In formulating oxandrolone, it is recognized that there may be differences between the immediate and the long term response. To account for these changes, the specific dosage given to a particular patient is based also on the individual patient's response. Preferably, oxandrolone is orally administered to the patient daily for a time period in the range of about 2 weeks to about 6 months.

Attenuation of the rate of muscle mass loss in a patient can be ascertained by comparing the patient's rate of weight loss before oxandrolone therapy with that after the administration of oxandrolone has been commenced. Alternatively, or in addition, the patient's urinary nitrogen level can be monitored, a well-known expedient. A decrease in the patient's urinary nitrogen level is indicative of a decrease in muscle mass loss.

Similarly, the maintenance of a relatively stable patient's total body potassium level, as well as an increase in the patient's total body potassium level, upon oxandrolone administration indicates that a therapeutically effective amount of oxandrolone is being administered. A patient's total body potassium level can be monitored, for example, as described in Kotler et al., **The American Journal of Clinical Nutrition**, 42:1255-1265 (December 1985) and Pierson, Jr., et al., **Am. J. Physiol.**, 246 (Renal Fluid Electrolyte Physiol. 15):F234-F239 (1984).

The route of administration can be oral, percutaneous, transdermal, sublingual, buccal, intravenous, intramuscular, or the like. Of these, oral administration is preferred. The patient's daily dose of the active ingredient preferably is in the range of about 7.5 milligrams, but may exceed 20 milligrams based on clinical response. This daily dose can be given in

tablet form as a single dose, or as plural divided doses, preferably 2 to 3 divided doses. The requisite daily dose can also be supplied continuously, for example, by a transdermal patch worn by the patient or intravenously. If the oxandrolone is administered orally, dosages in the range of about 2 to about 5 milligrams three to four times daily typically may be utilized.

Oxandrolone tablets are manufactured using standard solid dose form technology in accordance with United States Pharmacopeia (USP) specifications (see, for example, The United States Pharmacopeia, 22nd Revision, pp. 981-982). Specifically, a typical 150-milligram tablet contains the following:

Oxandrolone, USP	2.5 mg
Corn Starch, NF	30.0 mg
Lactose NF (hydrous)	113.0 mg
Hydroxypropyl Methylcellulose, USP	3.0 mg
Magnesium Stearate	1.5 mg
	150.0 mg

The terms "unit dosage form" and "unit dose" as used in the present specification and claims refer to a physically discrete unit or units suitable as unitary doses for patients, each unit containing a predetermined quantity of the active ingredient calculated to produce the desired therapeutic effect in association with the pharmacologically acceptable carrier. The specifications for the unit dosage forms of this invention are dictated in part and are also dependent upon (a) the unique characteristics of the active ingredient and (b) the particular therapeutic effect to be achieved, as well as upon limitations inherent in the art of compounding such active ingredient for the therapeutic use disclosed in detail in this specification. Examples of suitable unit dosage forms

in accordance with this invention are tablets, pills, powder packets, wafers, cachets, segregated multiples of any of the foregoing, transdermal patches, aliquots of injectables, and the like forms.

The primary response variables are patient's total body potassium, body weight, muscle mass, muscle strength, improvement in or increased appetite, and general sense of well-being. In addition, improvement in immune status (or at a minimum, no worsening of immune function) in response to oxandrolone is significant as well.

An important question regarding the use of any drug in combination with anti-retroviral therapy is whether drug interactions may occur that would diminish AZT efficacy or increase the frequency of severity of AZT-related adverse reactions. TABLE 1 compares various published pharmacological parameters for oxandrolone and AZT and illustrates important differences between the two drugs.

TABLE 1

Comparison of Selected Oxandrolone and AZT Pharmacology Parameters

Parameter	Oxandrolone	AZT
Oral Bioavailability	100%	65%
Tmax	1.1 hr	0.7 hr
Biological T1/2	9.4 hr	1.1 hr
Vd	578 ml/kg	>1400 ml/kg
Protein Binding	>95%	25-35%
Plasma Clearance	43 ml/kg/hr	>1300 ml/kg/hr
Metabolism	Little	Extensive
Glucuronidation	Little	Substantial
Urinary Excretion	Extensive; primarily parent compound	Extensive; parent and glucuronide conjugated
Target Organ Toxicity	Liver (anabolic steroids as a class)	Hematopoietic system (e.g., anemia, granulocytopenia)
Known Drug Interactions	Anticoagulants; oral hypoglycemic agents; adrenal steroid when edema present	Drugs that may: (a) inhibit glucuronidation (e.g., aspirin, acetaminophen) or urinary excretion (e.g., probenecid); (b) adversely affect blood cell number and function; and (c) nephrotoxic or cytotoxic

Because oxandrolone is primarily protein bound, whereas AZT is primarily non-protein bound, oxandrolone will not compete appreciably with AZT for binding sites in plasma. Consequently, administration of oxandrolone to patients on AZT therapy is unlikely to alter the level of free AZT in the blood. Likewise, the administration of AZT is unlikely to alter the level of free oxandrolone in the blood. An oxandrolone-AZT drug interaction involving binding site displacement is, therefore, extremely unlikely.

AZT is rapidly metabolized and excreted in the urine--a significant quantity is excreted in the form of glucuronide conjugates. In sharp contrast, oxandrolone, perhaps due to presence of a lactone group and the absence of a 4-ene function in the A-ring, undergoes little hepatic metabolism and is excreted primarily unchanged and unconjugated in urine. Thus, in contradistinction to other drugs that may competitively inhibit glucuronidation and thereby potentially slow the rate of AZT metabolism, such as aspirin, acetaminophen, or indomethacin, the present active agent, oxandrolone, is not believed to affect AZT metabolism.

Furthermore, oxandrolone is neither nephrotoxic nor cytotoxic. Accordingly, oxandrolone is not expected to interfere with the renal excretion of AZT or its metabolites. To the contrary, oxandrolone has been safely and effectively used in patients with chronic renal disease to stimulate growth and increase lean body mass. In well-controlled studies of oxandrolone for the clinical management of critically ill patients with acute alcoholic hepatitis, oxandr lone administered at daily doses of up to 80 mg/day for four weeks and 40 mg/day for eight weeks did not result in any drug-related nephrotoxicity.

While it is known that anabolic androgenic steroids have been associated with potentially life-threatening forms of liver disease, including peliosis hepatis, cholestatic jaundice, and hepatocellular neoplasms, specific reports in the medical literature regarding liver disease in oxandrolone-treated patients, at the dosages proposed for use in the clinical management of HIV associated muscle weakness/wasting (i.e., about 2.5 to about 20 mg/day) are rare.

Oxandrolone and AZT have different mechanisms of action. They also function in different sites of cellular action at the receptor level. Oxandrolone functions via interaction with androgen and glucocorticoid receptors, whereas AZT, once phosphorylated, acts to inhibit HIV reverse transcription. Thus, competitive inhibition of AZT by oxandrolone at the cellular level also is considered unlikely.

Neither has oxandrolone been associated with anemia or granulocytopenia, two frequently occurring and potentially serious side effects associated with AZT therapy. To the contrary, anabolic androgenic steroids have been used clinically to stimulate ethyropoiesis in hypoanemias, aplastic anemias, hemolytic anemias, renal anemias, anemias due to cytotoxic therapy, and various leukemias. It has been reported recently that androgens augment beneficial effects of erythropoietin in the treatment of anemia resulting from end-stage renal disease.

Data derived from animal models and human clinical studies indicate that anabolic steroids are unlikely to suppress immune function in patients infected with HIV. For example, anabolic steroids can stimulate granulopoiesis in mice, as evidenced by stimulation of granulocytic colony-forming cells derived

from spleen and bone marrow. Similarly, an anabolic steroid known as nandrolone decanonate enhanced macrophage activity and cell-mediated immunity in patients with uterine cervical cancer when administered parentally. In related studies, anabolic steroids increased peripheral lymphocyte and monocyte counts, Immunoglobin G (IgG) levels, and PHA-blastoid transformation of peripheral lymphocytes. In those studies, β_2-microglobulin levels simultaneously decreased.

IgG is one of a class of antibodies secreted by B cells (i.e., B-lymphocytes) in response to an antigenic challenge (e.g., foreign protein like that from bacteria). In the case of HIV infection, humoral immune function (i.e., B-cell mediated) is significantly impaired. Accordingly, when HIV-infected individuals are challenged with a specific antigen, the typical response of B-cell proliferation, differentiation and secretion of antibodies (e.g., IgG) is diminished or absent. This decline in humoral immune function coupled with defects in cellular immune (i.e., T-cell) function contributes to the overall failure of the immune system to respond in an appropriate manner to challenge. B-cells in AIDS victims are, by mechanisms unknown, hyperstimulated to secrete large amounts of immunoglobulins that make the humoral system refractory to new antigens. The result is that the patient's system no longer recognizes new antigens and does not respond.

In animal studies in which anabolic ster ids have been reported to increase IgG and PHA-blastoid activity, these changes occurred as a result of immune system stimulation, and are positive responses. β-microglobin is a cell surface protein that is found on all nucleated cells and it is released into the serum

during cell turnover. Generally, β-microglobulin is considered a marker of infectious, inflammatory, malignant and autoimmune disease activity. In several AIDS studies, β-microglobulin levels correlated with disease progression and T4 (T-helper) cell counts. In the case of therapy with oxandrolone, for example, a decrease in β-microglobulin levels is desirable. Thus, animal data showing reduced plasma levels of β-microglobulin in response to anabolic steroids is evidence of a positive effect and suggestive of similar activity in man.

Accordingly, there are no reasons to believe that the administration of an anabolic steroid in general and oxandrolone in particular would have adverse effects on the immune system. Generally, the target organ of toxicity for these drugs is the liver--probably because this is where most are metabolized. Oxandrolone, however, has a remarkably good safety profile in man as a likely consequence of its resistance to hepatic metabolism; an oral dose is excreted primarily in urine as the parent compound, as stated hereinabove.

Data from clinical trials in patients with severe alcoholic liver disease provide further evidence that oxandrolone is not likely to suppress immune function in patients with HIV infection. Ethanol abuse is associated with loss of lymphocyte functions, particularly T-cell dependent immune responses. Previous researchers have observed that oxandrolone significantly improved lymphocyte number in patients with severe alcoholic hepatitis. Because the loss of lymphocytic function by alcoholic liver disease parallels, to a significant degree, the loss of T-cell function due to HIV infection, it is reasonable to

hypothesize that oxandrolone will increase the T-Cell function of HIV-infected patients.

Therefore, these data from laboratory animals and human studies indicate that suppression of the immune system by anabolic steroids, such as oxandrolone, is unlikely. Nonetheless, subjects undergoing oxandrolone therapy, as a precaution, should be monitored for changes in lymphocyte number, particularly CD4+ and CD8+, as is routinely done for patients who undergo steroid therapy.

In summary, based on the differences between AZT and oxandrolone with respect to pharmacokinetics, metabolism, reported drug interactions, mechanisms of action, and reported toxicities, oxandrolone and AZT can be safely used in combination for subjects infected with the Type-1 HIV virus and suffering from HIV-associated myopathy. The use of oxandrolone in patients on AZT therapy is, on the basis of known drug interactions, also consistent with current FDA-approved labeling for AZT and oxandrolone.

The following example demonstrates the effectiveness of oxandrolone in attenuating the effects of HIV-associated muscle weakness or muscle wasting in an AIDS patient.

EXAMPLE

A patient, a thirty-two year old homosexual man, known to be HIV-seropositive since February 1989, noted difficulty opening drawers and bottles in May 1989. The patient weakened progressively and, during a physical examination in September 1989, demonstrated by confrontation testing the weakness of neck flexion and proximal limbs. However, his muscle stretch refl xes remained normal. Laboratory tests showed the patient's creatine kinase level to be 286 International Units per

liter, much higher than the normally observed range for creatine kinase of about 40-200 Units per liter.

Zidovudine (azidothymidine or AZT) was initiated at 500 milligrams daily, but the patient's strength continued to decline through February 1990. He complained of an inability to ascend a flight of stairs. The patient exhibited greater weakness and atrophy of neck flexors and extremity muscles during another physical examination performed at this time. An electromyogram revealed a decrease of amplitude and duration of the patient's motor unit potentials and increased recruitment in selected muscles of his right upper extremity. The patient's creatine kinase tested at 456 Units per liter. A muscle biopsy revealed numerous myofibers, abundant ragged red fibers, and numerous eosinophilic inclusions. Round cell inflammatory infiltrates were also noted. In light of these developments, the zidovudine treatment was terminated.

Substantial improvement initially followed the discontinuation of zidovudine. However, because of a subsequent continued and progressive weakness rendering it difficult for the patient to ascend or descend a flight of stairs, a prednisone therapy (60 mg daily) was initiated. No significant improvement accompanied the use of prednisone.

Thereafter, a trial period of oral oxandrolone administration (2.5 milligrams, three times daily, in tablet form) was initiated. Within two weeks of the initiation of the oxandrolone therapy, the patient not d an improved sense of well being, became stronger, and gained weight. Within one month, he was able to ascend and descend stairs without problems. Confrontation testing revealed nearly normal strength. The patient's weight increased from 115 pounds to 130 pounds. The

patient's muscle atrophy was alleviated as well. Liver functions were closely monitored for signs of elevation, but undesirable side effects were not detected.

After several months of the aforementioned therapy with oxandrolone, the patient was no longer able to obtain oxandrolone for use as a medication. Weakness and weight loss ensued. Trials of other anabolic preparations, specifically stanazol and oxymethalone, did not return the patient to his previous levels of function and strength.

The EXAMPLE demonstrates that oxandrolon can be a beneficial alternative for clinical management of HIV-associated myopathy and muscle weakness and wasting.

It is intended that the foregoing description is by way of illustration only and is not to be construed as limiting the invention in any way except in the spirit and scope of the appended claims.

WHAT IS CLAIMED IS:

1. Use of oxandrolone in the manufacture of a composition for the amelioration of myopathy and muscle weakness in an amount effective to attenuate the rate of muscle mass loss in a patient infected with a Type-1 human immunodeficiency virus.

2. The use of oxandrolone according to claim 1 wherein the oxandrolone is administered to the patient in a daily dosage in the range of about 2.5-30 milligrams.

3. The use of oxandrolone according to claim 2 wherein the oxandrolone is administered to the patient in a daily dosage of about 7.5 milligrams.

4. The use of oxandrolone according to claim 2 wherein the oxandrolone is administered to the patient in a daily dosage of about 15 milligrams.

5. The use of oxandrolone according to claim 1 wherein the oxandrolone is administered to the patient as a unit dose of about 1-5 milligrams 3 times a day at about eight hour intervals.

6. The use of oxandrolone according to claim 1 wherein the resulting composition is administered percutaneously.

7. The use of oxandrolone according to claim 1 wherein the resulting composition is administered intravenously.

8. The use of oxandrolone according to claim 1 wherein the resulting composition is administered intramuscularly.

9. The use of oxandrolone according to claim 1 wherein the resulting composition is administered sublingually.

10. The use of oxandrolone according to claim 1 wherein the resulting composition is administered transdermally.

11. The use of oxandrolone according to claim 1 wherein the resulting composition is administered orally.

12. The use of oxandrolone according to claim 11 wherein the resulting composition is in the form of a tablet.

13. The use of oxandrolone according to claim 1 wherein the resulting composition may be administered for a time period in the range of about 2 weeks to about 6 months.

14. Use of oxandrolone in the manufacture of a composition for the amelioration of myopathy and muscle weakness in a patient infected with a Type-1 human immunodeficiency virus such that the resulting composition may be an oral composition suitable for administration for a time period in the range of about 2 weeks to about 6 months.

15. A pharmaceutical composition comprising oxandrolone in an amount effective to attenuate the rate of muscle mass loss for the amelioration of myopathy and muscle weakness in a patient infected with a Type-1 human immunodeficiency virus and a pharmaceutically acceptable carrier.

16. The composition of claim 15 wherein the effective amount provides a daily dosage in the range of about 2.5 to about 30 milligrams oxandrolone.

17. The composition of claim 15 wherein the effective amount provides a daily dosage of about 7.5 milligrams oxandrolone.

18. The composition of claim 15 wherein the effective amount provides a daily dosage of about 15 milligrams oxandrolone.

19. The composition of claim 15 wherein the effective amount provides a unit dose of about 1 to about 5 milligrams oxandrolone and is administered 3 times per day at about equally spaced intervals.

20. The composition of claim 15 for percutaneous administration.

21. The composition of claim 15 for intravenous administration.

22. The composition of claim 15 for intramuscular administration.

23. The composition of claim 15 for sublingual administration.

24. The composition of claim 15 for transdermal administration.

25. The composition of claim 15 for oral administration.

26. The composition of claim 25 in the form of a tablet.

27. The composition of claim 15 for administration over a time period in the range of about 2 weeks to about 6 months.

28. A composition comprising oxandrolone for the amelioration of myopathy and muscle weakness in a patient infected with a Type-1 human immunodeficiency virus and a pharmaceutically acceptable carrier such

that the composition is an oral composition and is appropriate for administration for a time period in the range of about 2 weeks to about 6 months.

29. A method for ameliorating myopathy and muscle weakness in a patient infected with a Type-1 human immunodeficiency virus which comprises administering to said patient oxandrolone in an amount sufficient to attenuate the rate of muscle mass loss in said patient.

30. The method in accordance with claim 29 wherein the oxandrolone is administered to said patient in a daily dosage in the range of about 2.5 to about 30 milligrams.

31. The method in accordance with claim 29 wherein the daily dosage of the oxandrolone is about 7.5 milligrams.

32. The method in accordance with claim 29 wherein the daily dosage of the oxandrolone is about 15 milligrams.

33. The method in accordance with claim 29 wherein the oxandrolone is administered to said patient as a unit dose of about 1 to about 5 milligrams three times per day at about eight-hour intervals.

34. The method in accordance with claim 29 wherein the oxandrolone is administered percutaneously.

35. The method in accordance with claim 29 wherein the oxandrolone is administered intravenously.

36. The method in accordance with claim 29 wherein the oxandrolone is administered intramuscularly.

37. The method in accordance with claim 29 wherein the oxandrolone is administered sublingually.

38. The method in accordance with claim 29 wherein the oxandrolone is administered transdermally.

39. The method in accordance with claim 29 wherein the oxandrolone is administered orally.

40. The method in accordance with claim 39 wherein the oxandrolone is administered in the form of a tablet.

41. The method in accordance with claim 29 wherein administration is continued over a period in the range of about 2 weeks to about 6 months.

42. A method for ameliorating HIV-associated myopathy and muscle wasting in a patient infected with a Type-1 human immunodeficiency virus which comprises orally administering a therapeutically effective amount of oxandrolone to said patient daily for a time period in the range of about 2 weeks to about 6 months.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/10063

A. CLASSIFICATION OF SUBJECT MATTER
IPC(5) :A61K 31/585
US CL :514/175
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 514/175

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
none

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS, APS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Chemical Abstracts, Volume 74, no. 4, issued 17 May 1991, (Columbus Ohio, USA)), Bourse et al, "Comparison of the androgenic and myotrophic activities of some anabolic steroids in the castrated rat.", see abstract no. 72305d, (Res. Div., Hoffman-La Roche Inc., Nutley, N.J.) J. Steroid Biochem., 1970, vol.1 (4), pp. 349-54.	1-42

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be part of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Chemical Abstracts, Volume 115, no. 15, Issued 02 July 1991 (Columbus Ohio, U.S.A.)), Aroonsakul, Chaivanee, "Method of treatment of central nervous system diseases such as Alzheimer's disease and Parkinson's disease and method of diagnosing Alzheimer's disease",see abstract no. 151902q, Pat. Specif. (Aust.) AU 604,820 (Cl. A61K 31/565), 03 Jan. 1991, Appl. 88/10,125, 08 Jan 1988, 34pp.	1-42
Y	Chemical Abstracts, Volume 107, no. 18, Issued 27 September 1987, (Columbus Ohio, U.S.A.)), Lone et al, "The use of oxandrolone , an anabolic-androgenic steroid, as a growth promotant in carp. Effect on tissues molecular growth responses",see abstract nol 174950c, (Dep. Biol. Sci., Univ. Aston, Birmingham, UK B4 7ET). Pak J. Zool. 1986, vol. 18(2), pp. 153-69.	1-42

Form PTO-1449	U.S. Department of Commerce Patent and Trademark Office	Atty. Docket No. 4657-AAA-PCT-US	Serial No. Not Yet Kn wn
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INFORMATION DISCLOSURE CITATION (Use several sheets if necessary)		Filing Date Herewith	Group

U.S. PATENT DOCUMENTS

Examiner Initial		Document Number	Date	Name	Class	Subclass	Filing Date if Appropriate

FOREIGN PATENT DOCUMENTS

		Document Number	Date	Country	Class	Subclass	Translation	
							Yes	No
		0 2 2 2 3 8 5	February 3, 1993	Europe				

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

		Chicago Tribune, September 20, 1991, North Sports Final edition, Business Section, page 1
		Martindale, The Extra Pharmacopoeia, The Pharmaceutical Press, London, Reynolds, et al., Eds., p.1430 (1982)
		Physicians' Desk Reference (1988), 42nd Edition, cover page and pages 1975-1976
		PR Newswire, 0828P8715, August 28, 1991 "Gynex obtains international rights to drug to treat for growth disorders, AIDS"
		Aroonsakul, Chemical Abstracts, Vol. 115: 151902q, 1988
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		O'Shea, et al., Chemical Abstracts, Vol. 74: 75106a, 1971
		Kopera, H. Acta Endocrinologica 1985, Supplementum 271, pp. 11-18

EXAMINER	DATE CONSIDERED

*EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609: Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.